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THE UNITED STATES OF AMERICA

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March 31, 2005

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Under Secretary of Commerce
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030304

PROVISIONAL APPLICATION COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION under 37 CFR 1.53 (b)(2).

Docket Number		68051-A-Pro		Type a plus sign (+) inside this box →		+
INVENTOR(s)/APPLICANT(s)						
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TITLE OF THE INVENTION (280 characters max)						
COMBINATION THERAPY WITH GLATIRAMER ACETATE AND RILUZOLE FOR NEUROPROTECTION						
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STATE	NY	ZIP CODE	10036	COUNTRY	USA	
ENCLOSED APPLICATION PARTS (check all that apply)						
<input checked="" type="checkbox"/>	Specification	Number of Pages	53	<input type="checkbox"/>	Small Entity Statement	
<input type="checkbox"/>	Drawing(s)	Number of Sheets		<input checked="" type="checkbox"/>	Express Mail Certificate of Mailing bearing Label No. E7 735 978 992 US	
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22151 U.S. PTO
60/549975

030304

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☒ No.
☐ Yes, the name of the U.S. Government agency and the Government contract number are: _____

Respectfully submitted,

SIGNATURE

Date 03 /03 /04

TYPED or PRINTED NAME

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REGISTRATION NO.
(if appropriate)

39,992

☐ Additional inventors are being named on separately numbered sheets attached hereto

PROVISIONAL APPLICATION FILING ONLY

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Liat Hayardeny et al.

Serial No.: Not Yet Known

Filed : Herewith

For : COMBINATION THERAPY WITH GLATIRAMER ACETATE AND
RILUZOLE FOR NEUROPROTECTION

1185 Avenue of the Americas
New York, New York 10036
March 3, 2004

Mail Stop: Provisional Application
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D.C. 20231.

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**Application
for
United States Letters Patent**

To all whom it may concern:

Be it known that, we,

*Liat Hayardeny, Ety Klinger, Eran Blaugrund
have invented certain new and useful improvements in*

COMBINATION THERAPY WITH GLATIRAMER ACETATE AND RILUZOLE FOR NEUROPROTECTION

of which the following is a full, clear and exact description.

USE OF A COMBINATION OF RILUZOLE AND GLATIRAMER ACETATE
FOR NEUROPROTECTION

5

Throughout this application, various publications are referenced in parenthesis. Full citations for these publications may be found listed in alphabetical order at the end of the specification immediately preceding the claims. The disclosures
10 of these publications in their entireties are hereby incorporated by reference into this application in order to more fully describe the state of the art to which this invention pertains.

15 Field of the Invention

The subject invention relates to combination therapy for neuroprotection.

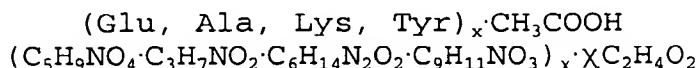
Background of the Invention

20 Neuroprotection refers to protection of the central or peripheral nervous system from neuronal loss, axonal loss and/or myelin loss. Providing neuroprotection is one way to effect the treatment of neurodegenerative conditions and neurotrauma.

25 Glatiramer acetate, also known as Copolymer 1 has been shown to be effective in treating multiple sclerosis (MS) (Lampert, P.W.). Daily subcutaneous injections of glatiramer acetate (20 mg/injection) reduce relapse rates, progression of disability, appearance of new lesions by magnetic resonance imaging (MRI),
30 (Johnson, K.P. et al.) and appearance of "black holes" (Filippi, M. et al.).

COPAXONE® is the brand name for a formulation containing glatiramer acetate as the active ingredient. Glatiramer acetate
35 is approved for reducing the frequency of relapses in relapsing-remitting multiple sclerosis. Glatiramer acetate consists of the acetate salts of synthetic polypeptides containing four

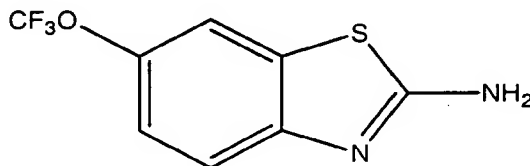
naturally occurring amino acids: L-glutamic acid, L-alanine, L-tyrosine, and L-lysine with an average molar fraction in COPAXONE® of 0.141, 0.427, 0.095 and 0.338, respectively. In COPAXONE®, the average molecular weight of the glatiramer acetate is 4,700-11,000 daltons. Chemically, glatiramer acetate is designated L-glutamic acid polymer with L-alanine, L-lysine and L-tyrosine, acetate (salt). Its structural formula is:



CAS - 147245-92-9.

The recommended dosing schedule of COPAXONE® for relapsing-remitting multiple sclerosis is 20 mg per day injected subcutaneously (Physician's Desk Reference, 2003; see also U.S. Patent Nos. 3,849,550; 5,800,808; 5,858,964; 5,981,589; 6,048,898; 6,054,430; 6,214,791; 6,342,476; and 6,362,161, all of which are hereby incorporated by reference).

Riluzole is a member of the benzothiazole class. Chemically, riluzole is 2-amino-6-trifluoromethoxy benzothiazole. Its molecular formula is $\text{C}_8\text{H}_5\text{F}_3\text{N}_2\text{OS}$ and its molecular weight is 234.2. Its structural formula is as follows:



and it has a molecular weight of 234.2 (Physician's Desk Reference, 2002).

RILUTEK® is a commercially available formulation of riluzole (2-amino-6-trifluoromethoxy benzothiazole), which is indicated for

the treatment of patients with amyotrophic lateral sclerosis (ALS). RILUTEK® extends survival and/or time to tracheostomy. The recommended dose for RILUTEK® is 50 mg every 12 hours. RILUTEK® should be administered at least one hour before or at
5 least two hours after a meal (Physician's Desk Reference, 2003).

The administration of two drugs to treat a given condition, such as a form of multiple sclerosis, raises a number of potential problems. *In vivo* interactions between two drugs are complex.
10 The effects of any single drug are related to its absorption, distribution, and elimination. When two drugs are introduced into the body, each drug can affect the absorption, distribution, and elimination of the other and hence, alter the effects of the other. For instance, one drug may inhibit,
15 activate or induce the production of enzymes involved in a metabolic route of elimination of the other drug (Guidance for Industry. *In vivo* drug metabolism/drug interaction studies - study design, data analysis, and recommendations for dosing and labeling). Thus, when two drugs are administered to treat the
20 same condition, it is unpredictable whether each will complement, have no effect on, or interfere with, the therapeutic activity of the other in a human subject.

Not only may the interaction between two drugs affect the
25 intended therapeutic activity of each drug, but the interaction may increase the levels of toxic metabolites (Guidance for Industry. *In vivo* drug metabolism/drug interaction studies - study design, data analysis, and recommendations for dosing and labeling). The interaction may also heighten or lessen the side
30 effects of each drug. Hence, upon administration of two drugs to treat a disease, it is unpredictable what change will occur in the negative side profile of each drug.

Additionally, it is accurately difficult to predict when the
35 effects of the interaction between the two drugs will become

manifest. For example, metabolic interactions between drugs may become apparent upon the initial administration of the second drug, after the two have reached a steady-state concentration or upon discontinuation of one of the drugs (Guidance for Industry.
5 *In vivo* drug metabolism/drug interaction studies - study design, data analysis, and recommendations for dosing and labeling).

Thus, the success of one drug or each drug alone in an *in vitro* model, an animal model, or in humans, may not correlate into
10 efficacy when both drugs are administered to humans.

In accordance with the subject invention, glatiramer acetate and 2-amino-6-trifluoromethoxybenzathiazole are effective in combination to provide neuroprotection in various
15 neurodegenerative diseases, including multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), acute disseminated encephalomyelitis, adrenleukodystrophy, adreno-myeloneuropathy, Leber's hereditary optic atrophy, Human Lymphotropic T-cell Virus I (HTLVI)-associated myelopathy, acute viral encephalitis,
20 aseptic meningitis, virus-induced demyelination, demyelinating genetic diseases, transverse myelitis, Progressive Multifocal Leucoencephalopathy, a nutritional metabolic disorder, acute glaucoma, chronic glaucoma, close-angle glaucoma, open-angle glaucoma, optic neuritis and systemic lupus erythematosus. The
25 use of glatiramer acetate and riluzole in combination according to the subject invention also provides neuroprotection in various neurotrauma resulting from a traumatic event, such as head trauma, spinal trauma, neurotoxic injury, eye injury, stroke, ischemia, hypoxia, and anoxia. Additionally according
30 to the subject invention, the use of glatiramer acetate and riluzole in combination provides neuroprotection including protection against toxic levels of glutamate or toxic levels of monoamine oxidase-B activity.

Summary of the Invention

The subject invention provides a method of providing neuroprotection to the central or peripheral nervous system of a subject in need of such neuroprotection comprising periodically administering to the subject an amount of glatiramer acetate and an amount of 2-amino-6-trifluoromethoxybenzathiazole, wherein the amounts when taken together are effective to provide neuroprotection to the central or peripheral nervous system of the subject.

In addition, the subject invention provides a package comprising

- i) a first pharmaceutical composition comprising an amount of glatiramer acetate and a pharmaceutically acceptable carrier;
- ii) a second pharmaceutical composition comprising an amount of 2-amino-6-trifluoromethoxybenzothiazole and a pharmaceutically acceptable carrier; and
- iii) instructions for use of the first and second pharmaceutical compositions together to provide neuroprotection to a subject.

The subject invention further provides a pharmaceutical composition comprising an amount of glatiramer acetate and an amount of 2-amino-6-trifluoromethoxybenzothiazole, wherein the amounts when taken together are effective to provide neuroprotection to a subject.

Detailed Description of the Invention

The subject invention provides a method of providing neuroprotection to the central or peripheral nervous system of a subject in need of such neuroprotection comprising periodically administering to the subject an amount of glatiramer acetate and an amount of 2-amino-6-trifluoromethoxybenzathiazole, wherein the amounts when taken together are effective to provide neuroprotection to the central or peripheral nervous system of the subject.

In one embodiment, providing neuroprotection comprises treating a neurodegenerative disease.

In an embodiment, the neurodegenerative disease is multiple sclerosis, amyotrophic lateral sclerosis, acute disseminated encephalomyelitis, transverse myelitis, demyelinating genetic diseases, virus-induced demyelination, Progressive Multifocal Leucoencephalopathy, Human Lymphotropic T-cell Virus I (HTLVI)-associated myelopathy, a nutritional metabolic disorder, acute glaucoma, chronic glaucoma, close-angle glaucoma, open-angle glaucoma, optic neuritis or systemic lupus erythematosus.

In a further embodiment, the neurodegenerative disease is multiple sclerosis.

In an additional embodiment, the neurodegenerative disease is amyotrophic lateral sclerosis.

In yet another embodiment, the neurodegenerative disease is acute close-angle glaucoma.

In one embodiment, the neurodegenerative disease is optic neuritis.

In a further embodiment, the neurodegenerative disease is systemic lupus erythematosus.

5 In an added embodiment, the neurodegenerative disease is a nutritional metabolic disorder.

In still another embodiment, the nutritional metabolic disorder is vitamin deficiency or central pontine myelinolysis.

10 In one embodiment, the vitamin deficiency is vitamin B₁₂ deficiency.

In an additional embodiment, providing neuroprotection comprises treating neurotrauma.

15

In a further embodiment, the neurotrauma is a result of a traumatic event selected from the group consisting of head trauma, spinal trauma, neurotoxic injury, eye injury, stroke, ischemia, hypoxia, and anoxia.

20

In another embodiment, the neurotrauma is a result of eye injury.

25 In one embodiment, providing neuroprotection comprises providing protection against toxic levels of glutamate.

In an added embodiment, the neuroprotection comprises protection against toxic levels of monoamine oxidase-B activity.

30 In another embodiment, the subject is a human being.

In a further embodiment, each of the amount of glatiramer acetate when taken alone, and the amount of 2-amino-6-trifluoromethoxybenzathiazole when taken alone is effective to

provide neuroprotection.

5 In an embodiment, either the amount of glatiramer acetate when taken alone, the amount of 2-amino-6-trifluoromethoxybenzathiazole when taken alone or each such amount when taken alone is not effective to provide neuroprotection.

10 In one embodiment, the amount of glatiramer acetate may be 10 to 80 mg; or 12 to 70 mg; or 14 to 60 mg; or 16 to 50 mg; or 18 to 40 mg; or 20 to 30 mg; or 20 mg. For each amount of glatiramer acetate, the amount of 2-amino-6-trifluoromethoxybenzathiazole may be 25 to 75 mg; or 35 to 65 mg; or 45 to 55 mg; or 50 mg.

15 Alternatively, the amount of glatiramer acetate may be in the range from 10 to 600 mg/week; or 100 to 550 mg/week; or 150 to 500 mg/week; or 200 to 450 mg/week; or 250 to 400 mg/week; or 300 to 350 mg/week; or 300 mg/week.

20 In another embodiment, the amount of glatiramer acetate may be in the range from 50 to 150 mg/day; or 60 to 140 mg/day; or 70 to 130 mg/day; or 80 to 120 mg/day; or 90 to 110 mg/day; or 100 mg/day.

25 Alternatively, the amount of glatiramer acetate may be in the range from 10 to 80 mg/day; or 12 to 70 mg/day; or 14 to 60 mg/day; or 16 to 50 mg/day; or 18 to 40 mg/day; or 19 to 30 mg/day; or 20 mg/day.

30 In one embodiment, the periodic administration of glatiramer acetate is effected daily.

35 In another embodiment, the periodic administration of glatiramer acetate is effected twice daily at one half the amount.

In an additional embodiment, the periodic administration of glatiramer acetate is effected once every 3 to 11 days; or once every 5 to 9 days; or once every 7 days; or once every 24 hours.

5

For each administration schedule of glatiramer acetate, the 2-amino-6-trifluoromethoxybenzathiazole may be administered once every 8 to 16 hours; or once every 10 to 14 hours; or once every 12 hours.

10

In an embodiment, the periodic administration of 2-amino-6-trifluoromethoxybenzathiazole is effected at least one hours before or at least two hours after a meal.

15

In a further embodiment, the administration of the glatiramer acetate substantially precedes the administration of the 2-amino-6-trifluoromethoxybenzathiazole.

20

In an added embodiment, the administration of the 2-amino-6-trifluoromethoxybenzathiazole substantially precedes the administration of the glatiramer acetate.

25

In one embodiment, the glatiramer acetate and the 2-amino-6-trifluoromethoxybenzathiazole may be administered for a period of time of at least 4 days. In a further embodiment, the period of time may be 5 days to 5 years; or 10 days to 3 years; or 2 weeks to 1 year; or 1 month to 6 months; or 3 months to 4 months. In yet another embodiment, the glatiramer acetate and the 2-amino-6-trifluoromethoxybenzathiazole may be administered for the lifetime of the subject.

30

The administration of 2-amino-6-trifluoromethoxybenzathiazole or glatiramer acetate may each independently be oral, nasal, pulmonary, parenteral, intravenous, intra-articular, transdermal, intradermal, subcutaneous, topical, intramuscular,

35

rectal, intrathecal, intraocular, buccal or by gavage. For 2-amino-6-trifluoromethoxybenzathiazole, the preferred route of administration is oral or by gavage. The preferred route of administration for glatiramer acetate is subcutaneous or oral.

5 One of skill in the art would recognize that doses at the higher end of the range may be required for oral administration.

In one embodiment, the administration of the glatiramer acetate may be subcutaneous, intraperitoneal, intravenous, 10 intramuscular, intraocular or oral and the administration of the 2-amino-6-trifluoromethoxybenzathiazole may be oral. In another embodiment, the administration of the glatiramer acetate may be subcutaneous and the administration of the 2-amino-6-trifluoromethoxybenzathiazole may be oral.

15

The subject invention also provides a package comprising

- i) a first pharmaceutical composition comprising an amount of glatiramer acetate and a pharmaceutically acceptable carrier;
- 20 ii) a second pharmaceutical composition comprising an amount of 2-amino-6-trifluoromethoxybenzothiazole and a pharmaceutically acceptable carrier; and
- iii) instructions for use of the first and second pharmaceutical compositions together to provide 25 neuroprotection to a subject.

In an embodiment of the package, the amount of glatiramer acetate may be in the range from 10 to 600 mg; or 100 to 550 mg; or 150 to 500 mg; or 200 to 450 mg; or 250 to 400 mg; or 300 to 30 350 mg; or 300 mg.

In another embodiment of the package, the amount of glatiramer acetate may be in the range from 10 to 80 mg; or 12 to 70 mg; or 14 to 60 mg; or 16 to 50 mg; or 18 to 40 mg; or 19 to 30 mg; or 35 20 mg.

Alternatively, the amount of glatiramer acetate in the package may be in the range from 50 to 150 mg; or 60 to 140 mg; or 70 to 130 mg; or 80 to 120 mg; or 90 to 110 mg; or 100 mg.

- 5 For each amount of glatiramer acetate in the package, the amount of 2-amino-6-trifluoromethoxybenzathiazole in the package may be 25-75 mg; or 35-65 mg; or 45-55 mg; or 50 mg.

10 In one embodiment of the package, providing neuroprotection comprises treating a neurodegenerative disease.

15 In another embodiment of the package, the neurodegenerative disease is multiple sclerosis, amyotrophic lateral sclerosis, acute disseminated encephalomyelitis, transverse myelitis, demyelinating genetic diseases, virus-induced demyelination, Progressive Multifocal Leucoencephalopathy, Human Lymphotropic T-cell Virus I (HTLVI)-associated myelopathy, a nutritional metabolic disorder, acute glaucoma, chronic glaucoma, close-angle glaucoma, open-angle glaucoma optic neuritis or systemic
20 lupus erythematosus.

In a further embodiment of the package, the nutritional metabolic disorder is vitamin deficiency or central pontine myelinolysis.

25

In yet another embodiment of the package, the vitamin deficiency is vitamin B₁₂ deficiency.

30 In an additional embodiment of the package, the neuroprotection comprises treatment of neurotrauma.

35 In one embodiment of the package, the neurotrauma is a result of a traumatic event selected from the group consisting of head trauma, spinal trauma, neurotoxic injury, eye injury, stroke, ischemia, hypoxia, and anoxia.

In a further embodiment of the package, the neuroprotection comprises protection against toxic levels of glutamate.

5 In still another embodiment of the package, the neuroprotection comprises protection against toxic levels of monoamine oxidase-B activity.

10 The subject invention further provides a pharmaceutical composition comprising an amount of glatiramer acetate and an amount of 2-amino-6-trifluoromethoxybenzothiazole, wherein the amounts when taken together are effective to provide neuroprotection to a subject.

15 In one embodiment of the pharmaceutical composition, each of the amount of glatiramer acetate when taken alone and the amount of 2-amino-6-trifluoromethoxybenzathiazole when taken alone is effective to provide neuroprotection.

20 In another embodiment of the pharmaceutical composition, either of the amount of glatiramer acetate when taken alone, or the amount of 2-amino-6-trifluoromethoxybenzathiazole when taken alone or each such amount when taken alone is not effective to provide neuroprotection.

25 In an embodiment of the pharmaceutical composition, providing neuroprotection comprises treating a neurodegenerative disease.

30 In a further embodiment of the pharmaceutical composition, the neurodegenerative disease is multiple sclerosis, amyotrophic lateral sclerosis, acute disseminated encephalomyelitis, transverse myelitis, demyelinating genetic diseases, virus-induced demyelination, Progressive Multifocal Leucoencephalopathy, Human Lymphotropic T-cell Virus I (HTLV I)-associated myelopathy, a nutritional metabolic disorder, acute

glaucoma, chronic glaucoma, close-angle glaucoma, open-angle glaucoma optic neuritis or systemic lupus erythematosus.

5 In another embodiment of the pharmaceutical composition, the nutritional metabolic disorder is vitamin deficiency or central pontine myelinolysis.

10 In an added embodiment of the pharmaceutical composition, the vitamin deficiency is vitamin B₁₂ deficiency.

In one embodiment of the pharmaceutical composition, the neuroprotection comprises treatment of neurotrauma.

15 In still another embodiment of the pharmaceutical composition, the neurotrauma is a result of a traumatic event selected from the group consisting of head trauma, spinal trauma, neurotoxic injury, eye injury, stroke, ischemia, hypoxia, and anoxia.

20 In an additional embodiment of the pharmaceutical composition, the neuroprotection comprises protection against toxic levels of glutamate.

25 In a further embodiment of the pharmaceutical composition, the neuroprotection comprises protection against toxic levels of monoamine oxidase-B activity.

30 The subject invention further provides a pharmaceutical combination comprising separate dosage forms of an amount of glatiramer acetate and an amount of 2-amino-6-trifluoromethoxybenzothiazole, which combination is useful to provide neuroprotection to a subject.

In an embodiment of the pharmaceutical combination, each of the amount of glatiramer acetate when taken alone and the amount of

2-amino-6-trifluoromethoxybenzathiazole when taken alone is provide neuroprotection.

5 In an additional embodiment of the pharmaceutical combination, either of the amount of glatiramer acetate when taken alone, the amount of 2-amino-6-trifluoromethoxybenzathiazole when taken alone or each such amount when taken alone is not effective to provide neuroprotection.

10 In a further embodiment, the pharmaceutical combination may be for simultaneous, separate or sequential use to provide neuroprotection to the subject.

15 In an embodiment of the pharmaceutical combination, providing neuroprotection comprises treating a neurodegenerative disease.

In still another embodiment of the pharmaceutical combination, the neurodegenerative disease is multiple sclerosis, amyotrophic lateral sclerosis, acute disseminated encephalomyelitis, 20 transverse myelitis, demyelinating genetic diseases, virus-induced demyelination, Progressive Multifocal Leucoencephalopathy, Human Lymphotropic T-cell Virus I (HTLVI)-associated myelopathy, a nutritional metabolic disorder, acute glaucoma, chronic glaucoma, close-angle glaucoma, open-angle 25 glaucoma optic neuritis or systemic lupus erythematosus.

In an embodiment of the pharmaceutical combination, the nutritional metabolic disorder is vitamin deficiency or central pontine myelinolysis.

30 In yet another embodiment of the pharmaceutical combination, the vitamin deficiency is vitamin B₁₂ deficiency.

In one embodiment of the pharmaceutical combination, the 35 neuroprotection comprises treatment of neurotrauma.

In another embodiment of the pharmaceutical combination, the neurotrauma is a result of a traumatic event selected from the group consisting of head trauma, spinal trauma, neurotoxic injury, eye injury, stroke, ischemia, hypoxia, and anoxia.

5

In a further embodiment of the pharmaceutical combination, the neuroprotection comprises protection against toxic levels of glutamate.

10 In still another embodiment of the pharmaceutical combination, the neuroprotection comprises protection against toxic levels of monoamine oxidase-B activity.

15 Providing neuroprotection includes protecting the central or peripheral nervous system from neurotrauma (U.S. Patent Nos. 6,271,263 and 6,277,886) and from neurodegenerative diseases (U.S. Patent Nos. 6,277,886). Neurotrauma is the damage to the central or peripheral nervous system caused by a traumatic event, such as head trauma, spinal trauma, neurotoxic injury, 20 stroke, ischemia, hypoxia, anoxia (U.S. Patent Nos. 6,277,886), or eye injury. Neurodegenerative diseases are diseases in which there is degeneration of the central or peripheral nervous system, such as multiple sclerosis (Lampert, P.W.), amyotrophic lateral sclerosis (Amyotrophic Lateral Sclerosis Information 25 Page), Alzheimer's disease, dementia (U.S. Patent Nos. 6,316,504 and 6,451,306), Parkinson's disease (U.S. Patent Nos. 6,395,546 and 6,451,306), acute disseminated encephalomyelitis, adrenleukodystrophy, adrenomyeloneuropathy, Leber's hereditary optic atrophy, Human Lymphotropic T-cell Virus (HTLV)- 30 associated myelopathy, acute viral encephalitis, aseptic meningitis (Merck Manual), optic neuritis (McKhann), glaucoma (U.S. Patent No. 6,444,676), and neuropathy.

In addition, providing neuroprotection encompasses providing

protection of the central or peripheral nervous system from
toxic levels of glutamate. Diseases which have been associated
with toxic levels of glutamate include ALS (Ask the pharmacist:
Common questions asked about Rilutek®), Huntington's disease
5 (Ashizawa) and systemic lupus erythematosus (Beckman).

Providing neuroprotection also includes providing protection
against toxic levels of monoamine oxidase-B (MAO-B) activity.
Diseases and conditions which have been associated with toxic
10 levels of monoamine oxidase-B are Parkinson's disease (Monoamine
oxidase B inhibitors. Current status and future potential;
Rationale for (-)deprenyl (Selegiline) therapy in Parkinson's
disease and Alzheimer's disease; Rodriguez-Gomez et al.),
Alzheimer's disease (Rationale for (-)deprenyl (Selegiline)
15 therapy in Parkinson's disease and Alzheimer's disease;
Monoamine oxidase B inhibitors. Current status and future
potential; Potential applications for monoamine oxidase B
inhibitors), memory disorders (The interaction of L-deprenyl and
scopolamine on spatial learning/memory in rats), depression
20 (Merck Manual of Diagnosis and Therapy; L-Deprenyl, a selective
monoamine oxidase type-b inhibitor in endogenous depression;
Potential applications for monoamine oxidase B inhibitors),
panic, post-traumatic stress disorder (PTSD), sexual
dysfunction, attention deficit and hyperactivity syndrome
25 (ADHD) (Potential applications for monoamine oxidase B
inhibitors), attention deficit disorder (Kleywegt), and
Tourette's syndrome (Treatment of Tourette's: Overview).

Formulations of the invention suitable for oral administration
30 may be in the form of capsules, pills, tablets, powders,
granules, or as a solution or a suspension in an aqueous or non-
aqueous liquid, or as an oil-in-water or water-in-oil liquid
emulsion, or as an elixir or syrup, or as pastilles (using an
inert base, such as gelatin and glycerin, or sucrose and acacia)
35 and/or as mouth washes and the like, each containing a

predetermined amount of the active compound or compounds.

In solid dosage forms of the invention for oral administration (capsules, tablets, pills, dragees, powders, granules and the like), the active ingredient(s) is mixed with one or more pharmaceutically acceptable carriers, such as sodium citrate or dicalcium phosphate, and/or any of the following: fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and/or silicic acid; binders, such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidone, sucrose and/or acacia; humectants, such as glycerol; disintegrating agents, such as agar-agar, calcium carbonate, calcium phosphate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate; solution retarding agents, such as paraffin; absorption accelerators, such as quaternary ammonium compounds; wetting agents, such as, for example, cetyl alcohol and glycerol monostearate; absorbents, such as kaolin and bentonite clay; lubricants, such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof; and coloring agents. In the case of capsules, tablets and pills, the pharmaceutical compositions may also comprise buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugars, as well as high molecular weight polyethylene glycols and the like.

Liquid dosage forms for oral administration of the active ingredients include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active ingredient(s), the liquid dosage forms may contain inert dilutents commonly used in the art, such as, for example, water or other solvents, solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate,

propylene glycol, 1,3-butylene glycol, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof.

5

Suspensions, in addition to the active compounds, may contain suspending agents such as ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, and mixtures thereof.

10

The pharmaceutical compositions, particularly those comprising glatiramer acetate, may also include human adjuvants or carriers known to those skilled in the art. Such adjuvants include complete Freund's adjuvant and incomplete Freund's adjuvant. The compositions may also comprise wetting agents, emulsifying and suspending agents, sweetening, flavoring, coloring, perfuming and preservative agents.

15

Glatiramer acetate may be formulated into pharmaceutical compositions with pharmaceutically acceptable carriers, such as water or saline and may be formulated into eye drops. Glatiramer acetate may also be formulated into delivery systems, such as matrix systems.

20

This invention will be better understood from the Experimental Details which follow. However, one skilled in the art will readily appreciate that the specific methods and results discussed are merely illustrative of the invention as described more fully in the claims which follow thereafter.

25

30

Experimental Details

EXAMPLE 1: GLUTAMATE TOXICITY

Under normal circumstances, glutamate functions as an essential neurotransmitter. However, when glutamate levels rise above the normal level, glutamate becomes toxic. Elevated glutamate levels and the resultant toxicity are implicated in many diseases, as discussed in the Background of the Invention.

Procedure

60 mice are injected with glutamate (0.2 M) to induce retinal ganglion cell (RGC) death. As shown in Table 1, mice are immunized with glatiramer acetate, riluzole or both prior to glutamate injection. Glatiramer acetate is given s.c. (subcutaneously), 100 μ l/mouse, with or without adjuvant. Glatiramer acetate can also be administered orally, with or without adjuvant. Glatiramer acetate may be administered over several doses before the glutamate challenge or may be administered simultaneously with glutamate. Riluzole is administered by gavage in 4 doses of 10 mg/kg each. The control animals receive PBS without any active agents, although any vehicle can be used.

Table 1: Administration Protocol

<u>Experimental Groups</u>	<u>Glatiramer Acetate</u>	<u>Riluzole</u>	<u>Glutamate</u>
A	X	X	X
B	X	-	X
C	-	X	X
D	-	-	X
E			

7 days after glutamate injection, mice are sacrificed, retinas are excised and surviving RGCs are counted. Following immunization, *in vitro* cellular response to specific activators,

such as glatiramer acetate, and to non-specific activators, such as Con-A, PHA, etc., are assessed.

Results

- 5 The administration of only glatiramer acetate (Group B) or only riluzole (Group C) prior to glutamate challenge raises the number of surviving RGCs above that of the control group that receives only glutamate (Group E). When both glatiramer acetate and riluzole are administered before the glutamate
- 10 administration (Group A), the number of surviving RGCs is comparable to or greater than the number of surviving RGCs in Group B (glatiramer acetate alone) or Group C (riluzole alone).

EXAMPLE 2: MPTP-INDUCED DOPAMINERGIC NEUROTOXICITY

MPTP is a neurotoxin that damages nigrostriatal dopaminergic neurons in several mammalian species, including mice, and produces a Parkinsonian syndrome in humans and primates. A
5 crucial initial step in the mechanism of its neurotoxicity involves conversion of MPTP to its toxic metabolite 1-methyl-4-phenyl pyridinium ion (MPP+). This reaction is catalyzed by the enzyme MAO-B and probably takes place outside of dopaminergic neurons, mainly in glia (U.S. Patent No. 6,316,504).

10

Procedure

i) Animals

Mice (C57Bl6 males weighing 20-25 g, 6-8 weeks of age) are obtained from Harlan (Jerusalem) and housed 5 per cage for 1
15 week before treatment. Standard mouse chow and water is supplied *ad libitum*. Room lighting is 12 hours light, 12 hours dark; lights on at 7:00 AM. The cages are maintained in a locked room in the animal house, accessible only to personnel familiar with the safety rules for MPTP administration, and wearing
20 appropriate protective clothing.

ii) Materials

Glatiramer acetate

Riluzole

25 MPTP hydrochloride, Sigma cat. # M0896, lot #89H4702

PBS: phosphate-buffered saline (g per liter): NaCl 8, KCl 0.2, Na₂HPO₄ 1.44, KH₂PO₄ 0.24; pH 7.4 (materials from Sigma, Israel)
sterile saline: NaCl, 0.9%

iii) Glatiramer acetate/riluzole administration

Table 2 presents the dosing schedule for the groups of mice (10 mice per group). 7 days before MPTP administration, the mice in Groups B, D and F are injected s.c. with 0.2 ml of a solution of glatiramer acetate (0.5 mg/ml) in PBS. This injection correlates to 100 µg/mouse. This dose is used because it has been used in other studies (glutamate toxicity, retinal intraocular pressure (IOP) model). Riluzole (10 mg/kg) is administered by gavage to the mice in Groups B, E and F 30 minutes before each of 4 MPTP injections. The members of control group A are injected s.c. with 0.2 ml of PBS and do not receive MPTP. The mice in control group B are injected s.c. with glatiramer acetate (100 µg/mouse) and given riluzole (10 mg/kg) by gavage, and saline instead of MPTP. The mice in control group C are injected s.c. with 0.2 ml of PBS followed by MPTP administration as outlined below.

Table 2: Administration Protocol

<u>Experimental Groups</u>	<u>GA</u>	<u>Riluzole</u>	<u>MPTP</u>
A			
B	X	X	
C			X
D	X		X
E		X	X
F	X	X	X

iv) MPTP administration

For the mice that have received glatiramer acetate, 7 days after glatiramer acetate immunization, cage bedding is changed and MPTP treatment is commenced. MPTP is obtained from Sigma in the form of 10 mg pre-weighed vials. The vial contents are dissolved in 2 ml sterile saline solution (0.9%) to yield a solution containing 5 mg/ml MPTP. Each mouse is injected

intraperitoneally (i.p.) with 0.1 ml of this solution per 20 g body weight, to give a dose of 25 mg per kg body weight. A total of 4 injections are given to each mouse, on each of 4 successive days, injections being made between 10 AM and 12 noon. Control
5 animals receive the same volume of sterile saline (0.1 ml per 20 g body weight).

v) Precautions during use of MPTP

Personnel wear disposable laboratory coats, disposable latex
10 rubber gloves and carbon filter face masks for the administration of MPTP. Cage bedding and all utensils in contact with MPTP is exposed to a 20% Clorox® solution (commercial bleach) for 30 minutes before containment in biohazard grade disposable nylon bags.

15

vi) Clinical assessment

Mice are observed for 30 minutes following each injection of MPTP.

20 vii) Determination of striatal dopamine

Mice are sacrificed by cervical dislocation 7 days after the first MPTP injection. Brains are removed and cooled on ice. Each whole brain is placed on its dorsal surface on an ice-cooled glass plate. A coronal cut is made with a razor blade at the
25 level of the optic chiasm. Striata is dissected from the frontal part of the brain and snap-frozen in liquid nitrogen, then stored at -70°C until homogenization.

Immediately prior to homogenization, the tissue is weighed. The
30 vials are removed from the -70°C refrigerator and quickly placed in a liquid nitrogen container. Taking care to keep the cap closed, each vial is then separately removed from the liquid nitrogen container. The frozen tissue is then quickly and carefully removed from the vial and placed on a pre-weighed dish
35 in the analytical balance. The tissue is then weighed.

For homogenization, the tissue is placed in an Ependorff tube to which 300 μ l of a 0.1 M perchlorate solution containing 2 mM sodium metabisulfite and 0.25 mM ethylenediaminetetracetic acid (EDTA) is added. The tissue is homogenized for 30 seconds in ice
5 using an Ependorff miniature homogenizer. Then, 300 μ l perchlorate is added (0.6 ml for more than 20 mg tissue).

The tissue is then centrifuged at 13000 g for 5-7 minutes and the supernatant is decanted for catecholamine determination. If
10 the analysis is not done on the same day, the samples can be frozen at -70°C and centrifuged again after thawing before analysis.

To detect the presence and amounts of dopamine, DOPAC and HVA, a hypersil H3ODS column (packing 3 mm, 4.6 mm diameter, 12.5 cm long) is used. The mobile phase is composed of NaH_2PO_4 100 mM, octan-1-sulphonic acid 1.5 mM, disodium ethylenediaminetetracetic acid 250 μ M, methanol 2.3%, and acetonitrile 4% in HPLC grade deionized water, at a flow rate of
20 1.0 ml min^{-1} . Compounds are detected with an ESA Coulochem model 5014 electrochemical detector (Bedford, MA, USA). Column eluates are initially oxidized by an ESA guard cell (model 5020) at +300 mV, then reduced at +60 mV at detector 1 and measured at detector 2 at -350 mV. The catecholamines are compared to
25 standards (10^{-7}M prepared in perchlorate). Dilution of the sample (1:10) for the dopamine determination might be needed. Levels of dopamine and metabolites are expressed in terms of pmol per mg tissue (frozen weight).

30 Results

In the absence of MPTP (Groups A and B), striatal dopamine levels are around 60-90 pmol/mg tissue. The administration of MPTP reduces the striatal dopamine levels to around 25-45 pmol/mg tissue (Group C). Immunization with glatiramer acetate
35 alone (Group D) prior to the administration of MPTP increases

the striatal dopamine levels. The administration of riluzole alone (Group E) before MPTP challenge increases the striatal dopamine levels. In Group F, the combined administration of glatiramer acetate and riluzole before injection of MPTP results
5 striatal dopamine levels that are comparable to or greater than the striatal dopamine levels of Group D (glatiramer acetate alone) or Group E (riluzole alone).

EXAMPLE 3: EXPERIMENTAL MODEL FOR AMYOTROPHIC LATERAL SCLEROSIS

Procedure

5 Transgenic mice carrying multiple copies of the human G93A Cu/Zn SOD mutation are considered to be the best model system for anterior horn cell degenerations such as amyotrophic lateral sclerosis (Ludolph et al.; Gurney et al. 1994 and 1996).

i) Animals

10 Transgenic mice overexpressing human Cu/Zn-SOD G93A mutations ((B6SJL-TgN (SOD1-G93A) 1 Gur) and non-transgenic B6/SJL mice are purchased from Jackson Laboratories (Bar Harbor, ME, USA). The second generation of G1H mice are used.

ii) Treatment Protocol

15 The SOD1 transgenic mice are treated in five groups (N = 15) with two dosages of glatiramer acetate alone or in combination with riluzole. A group of 15 mice serve as controls.

Treatment protocols for the six groups were the following:

- Group I: Low dose glatiramer acetate
- Group II: High dose glatiramer acetate
- 20 Group III: Riluzole 30 mg /kg per day
- Group IV: Low dose glatiramer acetate and riluzole 30 mg/kg per day
- Group V: High dose glatiramer acetate 2.0 mg/kg and riluzole 30 mg/kg per day
- 25 Group VI: Controls (placebo)

The drugs are administered in drinking water starting at 60 days of age.

iii) Survival

The clinical condition of the mice is monitored daily starting at 40 days. The onset of clinical signs is scored by examining the mice for tremors and/or shaking of the limbs, the position of one or both hind limbs (hanging rather than splaying out) when the mice are suspended in the air by their tail. The age of clinical onset was determined by the age (days) at which loss of splay or tremors of hind limbs is observed. The loss of righting reflex determines the end stage of the disease. The mice are sacrificed if they could not right themselves within 30 seconds when placed on either side on a flat surface.

iv) Behavior and Weight Assessment

Mice are observed daily (including weekends) and weighed weekly. Motor performance is assessed from 40 days of age using the rotarod apparatus to measure the night activity of the mice from 8 p.m. - 8 a.m. (LMTB, Berlin).

v) Neuropathological Studies

Mice were perfused transcardially with 4% paraformaldehyde/0.9% NaCl solution, brains and whole spinal cord were dissected out, frozen in liquid nitrogen and cut in transverse sections of 20 μ m on a sliding microtome. Sections of brainstem and spinal cord were stained with HE, toluidine blue (semi-thin sections, 0.5 μ m), and immunohistochemistry to label astrocytes (GFAP), cholinergic motoneurons (ChAT) and dopaminergic cells (TH).

Results

i) Survival

The primary end point of this study is survival. Animals treated with the low dose of glatiramer acetate alone show an increase in life span which is not statistically significant. The high dose of glatiramer acetate produces a statistically significant increase in life span. Both combinations of

riluzole and glatiramer acetate result in an increase in life span which is comparable to or greater than the increase in life span in the groups receiving only glatiramer acetate.

ii) Behavior

5 The results of measurements of running wheel activity in the 6 groups are largely complementary to the survival data. Statistical analysis show that glatiramer acetate-treated (at both dosages) and riluzole-treated animals are more active during the course of treatment and maintain their motor activity
10 longer than controls. Treatment with riluzole combined with either low-dose or high-dose glatiramer acetate results in activity comparable to or greater than treatment with riluzole alone or glatiramer acetate alone.

15 iii) Neuropathological Studies

Neuropathological examination of the spinal cord shows the typical features of G93A-associated damage; i.e. loss of motor neurons, astrocytosis and extensive vacuolation of the spinal grey matter. At the light-microscopic level, there are no
20 differences in the degree of neuronal loss, the morphology of astrocytosis or the extent of vacuolisation between animals. This lack of effect on histopathology may be due to the fact that all the animals are sacrificed at terminal stages of the disease.

EXAMPLE 4: CLINICAL TRIAL FOR ALZHEIMER'S DISEASE

Procedure

5 A double-blind clinical trial is conducted on patients with
Alzheimer's disease. Glatiramer acetate and riluzole (50 mg
b.i.d. (twice daily), oral) are administered to 20 patients
selected at random. Another group of 20 patients receive
placebo following the same dosage schedule as the treatment
10 group. Mental function (ability to process information and
short-term and long-term memory) is assessed monthly for a year
by standard clinical and laboratory tests. The inclusion and
exclusion criteria for patients are determined according to
medically accepted standards.

15 Results

In the clinical and laboratory tests, the group receiving
glatiramer acetate and riluzole shows improved ability to
process information and ability to recall information in the
short term and the long-term as compared to the group receiving
20 placebo.

EXAMPLE 5: CLINICAL TRIAL FOR PARKINSON'S DISEASE

Procedure

A double-blind clinical trial is conducted on patients with
5 Parkinson's disease. Sinemet® (Carbidopa-Levodopa) is
administered to each patient according to the dosing schedule
determined by medically acceptable standards to be most
appropriate for that patient. In addition to Sinemet®,
10 glatiramer acetate and riluzole (50 mg b.i.d. (twice daily),
oral) are administered to 20 patients selected at random.
Another group of 20 patients receive a placebo according to the
same dosing schedule, in addition to Sinemet®. The following
parameters are measured at entry into the trial and assessed
monthly for a year thereafter: measurement on Alzheimer's
15 Disease Assessment Scale - Cognitive Subscale (ADAS-cog),
cognitive function (ability to process information and short-
term and long-term memory), daily activities, and mood. The
inclusion and exclusion criteria for patients are determined
according to medically accepted standards.

20

Results

The administration of both glatiramer acetate and riluzole along
with Sinemet® produces results that are comparable to or greater
than those of the control groups receiving only Sinemet® for all
25 parameters tested - measurement on Alzheimer's Disease
Assessment Scale - Cognitive Subscale (ADAS-cog), cognitive
function (ability to process information and short-term and
long-term memory), daily activities, and mood.

EXAMPLE 6: CLINICAL TRIAL FOR GLAUCOMA

Procedure

5 Separate double-blind clinical trial are conducted on patients with the following types of glaucoma: i) acute close-angle glaucoma; ii) chronic close-angle glaucoma; iii) acute open-angle glaucoma; iv) chronic open-angle glaucoma

10 In each trial, glatiramer acetate and riluzole (50 mg b.i.d. (twice daily), oral) are administered to 20 patients selected at random. Another group of 20 patients receive placebo following the same dosage schedule as the treatment group. Intraocular pressure (IOP) is measured and a visual field test is performed at entry into the trial and assessed every two weeks for a year.
15 The inclusion and exclusion criteria for patients are determined according to medically accepted standards.

Results

20 In each trial, the administration of glatiramer acetate and riluzole results in a comparable or greater reduction of intraocular pressure than the administration of placebo. Additionally, the patients receiving glatiramer acetate and riluzole showed a comparable or greater improvement in the visual field test in comparison to the patients receiving
25 placebo.

EXAMPLE 7: CLINICAL TRIAL FOR HEAD INJURY

Procedure

A double-blind clinical trial is conducted on patients with head
5 injury. Glatiramer acetate and riluzole (50 mg b.i.d. (twice
daily), oral) are administered to 20 patients selected at
random. Another group of 20 patients receive placebo following
the same dosage schedule as the treatment group. The following
parameters are determined at entry into the trial and assessed
10 every two to four weeks for the first three months, monthly for
the next three months and then every two months for the next six
months: mental function (vocabulary, problem solving, memory),
mood, motor coordination, development of epilepsy, and length of
survival. The inclusion and exclusion criteria for patients are
15 determined according to medically accepted standards.

Results

In comparison to the controls, patients being treated with
glatiramer acetate and riluzole exhibit comparable or greater
20 mental function (vocabulary, problem solving, memory) and motor
coordination. In addition, the treatment group shows comparable
or better moods and comparable or greater survival time than the
controls. The patients who receive glatiramer acetate and
riluzole also demonstrate a comparable or greater reduction in
25 development of epilepsy than the controls.

EXAMPLE 8: CLINICAL TRIAL OF SPINAL CORD INJURY

Procedure

5 A double-blind clinical trial is conducted on patients with spinal cord injury. Glatiramer acetate and riluzole (50 mg b.i.d. (twice daily), oral) are administered to 20 patients selected at random. Another group of 20 patients receive placebo following the same dosage schedule as the treatment group. The following parameters are determined at entry into
10 the trial and assessed every two to four weeks for the first three months, monthly for the next three months and then every two months for the next six months: muscular spasms and ability to control affected muscles, including motor function, sexual function and bladder and bowel control. The inclusion and
15 exclusion criteria for patients are determined according to medically accepted standards.

Results

20 The administration of glatiramer acetate and riluzole result in comparable or greater ability to control affected muscles (motor function, sexual function and bladder and bowel control) than the administration of placebo. Treatment with glatiramer acetate and riluzole also results in a comparable or greater reduction in muscular spasms in comparison to placebo treatment.

25

EXAMPLE 9: CLINICAL TRIAL OF STROKE

Experiment 9i): Ischemic Stroke - Clinical Procedure

5 A double-blind clinical trial is conducted on patients with
ischemia. Glatiramer acetate and riluzole (50 mg b.i.d. (twice
daily), oral), and an anti-coagulant at its medically accepted
dose are administered to 20 patients selected at random.
10 Another group of 20 patients receive placebo and the anti-
coagulant following the same dosage schedule as the treatment
group. The following parameters are determined at entry into
the trial and assessed every one to four weeks for the first
three months and monthly for the next nine months: score on NIH
stroke scale, cognitive function (ability to process information
15 and short-term and long-term memory), and infract volume by MRI
and CT scan. The inclusion and exclusion criteria for patients
are determined according to medically accepted standards.

Experiment 9ii): Hemorrhagic Stroke - Clinical Procedure

20 The procedure of Experiment 10i) is followed except that the
patients are suffering from hemorrhagic stroke and an anti-
coagulant is not administered.

25 Results of Experiments 9i) and 9ii)

In both clinical trials, patients receiving glatiramer acetate
and riluzole show a comparable or greater score on the NIH
stroke scale and cognitive function (ability to process
information and short-term and long-term memory) as compared to
30 the controls. Additionally, the administration of glatiramer
acetate and riluzole results in a comparable or greater
reduction volume of infracts than the controls.

EXAMPLE 10: CLINICAL TRIAL OF ANOXIA/HYPOXIA

Procedure

5 A double-blind clinical trial is conducted on patients suffering
from axonia or hypoxia. Glatiramer acetate and riluzole (50 mg
b.i.d. (twice daily), oral) are administered to 20 patients
selected at random. Another group of 20 patients receive
placebo following the same dosage schedule as the treatment
group. Assessment of neurological function (Bayley II scale and
10 other tests), behavior (HOME and NCAST) and MRI (qualitative and
quantitative sensorimotor studies) are conducted on a monthly
basis for a year. The inclusion and exclusion criteria for
patients are determined according to medically accepted
standards.

15

Results

In comparison to the controls, the patients receiving glatiramer
acetate and riluzole exhibit comparable or greater neurological
function and behavior. Additionally, the MRI images of the
20 treatment group show a comparable or greater reduction in
abnormalities than the control group.

EXAMPLE 11: CLINICAL TRIAL OF DEMYELINATING DISEASE

Separate double-blind clinical trial are conducted on patients with the following demyelinating diseases: i) acute disseminated encephalomyelitis; ii) adrenleukodystrophy; iii) adrenomyeloneuropathy; iv) Leber's hereditary optic atrophy; v) Human Lymphotropic T-cell Virus 1 (HTLV-1)-associated myelopathy; vi) acute viral encephalitis; and vii) aseptic meningitis.

Procedure

In each trial, glatiramer acetate (20 mg/day, subcutaneous) and riluzole (50 mg b.i.d. (twice daily), oral) are administered to 20 patients selected at random. Another group of 20 patients receive glatiramer acetate (20 mg/day, subcutaneous) and placebo (50 mg b.i.d. (twice daily), oral). The following outcomes are measured: 1) Number of documented relapses; 2) Differences in mean change in EDSS (extended disability status scale); 3) Number of new T1 gadolinium (Gd) enhancing lesions; 5) Volume of T1-Gd enhancing lesions; 4) Total number of new T2 lesions; 5) Volume of T2 lesions; 6) Volume and number of hypointense lesions in T1 scans. Clinical assessments take place every 3 months (EDSS, T25W, AI). Lab tests and MRI are performed at the beginning of the study (baseline), then months 3, 6 and 12. The inclusion and exclusion criteria for patients are determined according to medically accepted standards.

Results

For all clinical trials, patients receiving glatiramer acetate and riluzole show a comparable or greater reduction in T1 and T2 Gd-enhancing lesions and other lesions in comparison to the controls. The administration of glatiramer acetate and riluzole results in a comparable or greater reduction in the number of relapses per year as compared to the controls.

EXAMPLE 12: CLINICAL TRIAL OF MULTIPLE SCLEROSIS

The purpose of this trial is to compare the treatment of participants with relapsing-remitting multiple sclerosis (RR-MS) with COPAXONE® in combination with riluzole, with treatment with COPAXONE® in combination with placebo. The clinical objective is to evaluate the effect of treatments on MRI variables, clinical evaluations and immunological profile.

The design of this trial is a randomized, double-masked, 2-arm study of COPAXONE® in combination with riluzole versus COPAXONE® in combination with placebo for the treatment of relapsing-remitting multiple sclerosis. Twenty patients with RR-MS who meet the inclusion/exclusion criteria are enrolled per arm. Patients are randomized and receive either 20 mg SQ (subcutaneous) of COPAXONE® daily plus an oral dose of placebo daily or 20 mg SQ of COPAXONE® in combination with 50 mg riluzole every 12 hours. The riluzole is administered at least one hour before a meal or at least two hours after a meal.

Participant inclusion criteria are as follows: 1) men or women age 18 to 50 years; 2) RR-MS according to the guidelines from the International Panel on the Diagnosis of MS (McDonald et al.); 3) two separate documented relapses in the last two years; 4) active MRI with at least one gadolinium(Gd)-enhancing lesion in the MRI scan at screening; 5) EDSS (extended disability status scale) score between 1.0 and 5.0; 6) no relapse during screening period; 6) pre-treatment with COPAXONE® for at least three weeks, but no more than four weeks, prior to baseline visit; and 7) ability to understand and provide informed consent.

Participant exclusion criteria include the following: 1) normal brain MRI; 2) prior treatment with COPAXONE® other than the scheduled three to four week pretreatment prior to baseline

visit; 3) previous treatment with immunomodulating agents such as interferon beta or IVIg for the last 6 months prior to entry; 4) previous use of immunosuppressive agents (including azathioprine) in the last 12 months prior study entry; 5) steroid treatment one month prior to entry; 6) women not willing to practice reliable methods of contraception; 7) pregnant or nursing women; 8) life threatening or clinically significant diseases; 9) history of alcohol and drug abuse within 6 months prior enrollment; 10) known history of sensitivity to Gd; 11) uncontrolled and uncontrollable head movements (tremor, tics, etc.), muscle spasms, significant urinary urgency and claustrophobia, which will prevent the subject from lying still during the MRI scan; and 12) participation in other investigational therapy in the last 90 days.

MRI scans are performed during the screening visit (for eligibility) and at months 5, 10, 11 and 12. Full physical and neurological examinations are performed at screening, baseline and at months 2, 5, 9 and 12. Safety laboratory is performed at screening baseline and at months 1, 2, 5, 9 and 12. In addition, blood Ca^{+} levels are monitored on the first and second months after baseline visit. The immunological profile is monitored at baseline and at months 1, 2, 4, and 5.

Primary efficacy endpoints include the following: 1) MRI variables as measured on months 10, 11, and 12; 2) total number and volume of T1 GD-enhanced lesions; 3) total number of new T2 lesions; and 4) total volume of T2 lesions. Secondary efficacy endpoints encompass the following: 1) changes in immunological parameters; and 2) PBMC proliferation in response to GA in vitro. The tertiary efficacy endpoints are as follows: 1) change from baseline in relapse rate and MS Functional Composite Score (MSFC); and 2) brain atrophy. Tolerability is evaluated with reference to the following: 1) percentage of subjects who discontinue the study; and 2) percentage of subjects who

discontinue the study due to adverse events. Safety is evaluated with reference to 1) adverse event frequency and severity; 2) changes in vital signs and 3) clinical laboratory values.

5

Patients treated with the COPAXONE® and riluzole combination exhibit a comparable or greater reduction in T1 and T2 Gd-enhancing lesions and other lesions, as compared to the group receiving COPAXONE® and placebo. Additionally, the group receiving the COPAXONE® and riluzole combination demonstrate a comparable or greater reduction in the number of relapses per year as compared with the group receiving COPAXONE® and placebo.

10

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What is Claimed:

1. A method of providing neuroprotection to the central or peripheral nervous system of a subject in need of such
5 neuroprotection comprising periodically administering to the subject an amount of glatiramer acetate and an amount of 2-amino-6-trifluoromethoxybenzathiazole, wherein the amounts when taken together are effective to provide neuroprotection to the central or peripheral nervous system of the subject.
- 10 2. The method of claim 1, wherein providing neuroprotection comprises treating a neurodegenerative disease.
- 15 3. The method of claim 2, wherein the neurodegenerative disease is multiple sclerosis, amyotrophic lateral sclerosis, acute disseminated encephalomyelitis, adrenleukodystrophy, adrenomyeloneuropathy, Leber's hereditary optic atrophy, Human Lymphotropic T-cell Virus I (HTLVI)-associated myelopathy, acute viral encephalitis, aseptic meningitis, virus-induced
20 demyelination, demyelinating genetic diseases, transverse myelitis, Progressive Multifocal Leucoencephalopathy, a nutritional metabolic disorder, acute glaucoma, chronic glaucoma, close-angle glaucoma, open-angle glaucoma, optic neuritis or systemic lupus erythematosus.
- 25 4. The method of claim 3, wherein the neurodegenerative disease is multiple sclerosis.
- 30 5. The method of claim 3, wherein the neurodegenerative disease is amyotrophic lateral sclerosis.
6. The method of claim 3, wherein the neurodegenerative disease is acute close-angle glaucoma.
- 35 7. The method of claim 3, wherein the neurodegenerative disease

is optic neuritis.

8. The method of claim 3, wherein the neurodegenerative disease is systemic lupus erythematosus.

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9. The method of claim 1, wherein providing neuroprotection comprises treating neurotrauma.

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10. The method of claim 9, wherein the neurotrauma is a result of a traumatic event selected from the group consisting of head trauma, spinal trauma, neurotoxic injury, eye injury, stroke, ischemia, hypoxia, and anoxia.

15

11. The method of claim 10, wherein the neurotrauma is a result of eye injury.

20

12. The method of claim 1, wherein providing neuroprotection comprises providing protection against toxic levels of glutamate.

13. The method of claim 1, wherein providing neuroprotection comprises providing protection against toxic levels of monoamine oxidase-B activity.

25

14. The method of claim 1, wherein the subject is a human being.

30

15. The method of claim 1, wherein each of the amount of glatiramer acetate when taken alone, and the amount of 2-amino-6-trifluoromethoxybenzathiazole when taken alone is effective to provide neuroprotection to the central or peripheral nervous system of the subject.

16. The method of claim 1, wherein either the amount of glatiramer acetate when taken alone, the amount of 2-amino-6-

trifluoromethoxybenzathiazole when taken alone or each such amount when taken alone is not effective to provide neuroprotection to the central or peripheral nervous system of the subject.

5

17. The method of claim 1, wherein the amount of glatiramer acetate is in the range from 10 to 600 mg/week.

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18. The method of claim 17, wherein the amount of glatiramer acetate is 300 mg/week.

19. The method of claim 1, wherein the amount of glatiramer acetate is in the range from 50 to 150 mg/day.

15

20. The method of claim 19, wherein the amount of glatiramer acetate is 100 mg/day.

21. The method of claim 1, wherein the amount of glatiramer acetate is in the range from 10 to 80 mg/day.

20

22. The method of claim 21, wherein the amount of glatiramer acetate is 20 mg/day.

25

23. The method of claim 1, wherein the periodic administration of glatiramer acetate is effected daily.

24. The method of claim 1, wherein the periodic administration of glatiramer acetate is effected twice daily at one half the amount.

30

25. The method of claim 1, wherein the periodic administration of glatiramer acetate is effected once every 5 to 9 days.

35

26. The method of claim 1, wherein the periodic administration of 2-amino-6-trifluoromethoxybenzathiazole is effected at least

one hours before or at least two hours after a meal.

27. The method of claim 1, wherein the administration of the
glatiramer acetate substantially precedes the administration of
5 the 2-amino-6-trifluoromethoxybenzathiazole.

28. The method of claim 1, wherein the administration of the 2-
amino-6-trifluoromethoxybenzathiazole substantially precedes the
administration of the glatiramer acetate.

10

29. The method of claim 1, wherein the administration of the
glatiramer acetate is effected subcutaneously,
intraperitoneally, intravenously, intramuscularly, intraocularly
or orally and the administration of the 2-amino-6-
15 trifluoromethoxybenzathiazole is effected orally.

30. The method of claim 29, wherein the administration of the
glatiramer acetate is effected subcutaneously and the
administration of the 2-amino-6-trifluoromethoxybenzathiazole is
20 effected orally.

31. A package comprising

- i) a first pharmaceutical composition comprising an
amount of glatiramer acetate and a pharmaceutically
25 acceptable carrier;
- ii) a second pharmaceutical composition comprising an
amount of 2-amino-6-trifluoromethoxybenzothiazole and
a pharmaceutically acceptable carrier; and
- iii) instructions for use of the first and second
30 pharmaceutical compositions together to provide
neuroprotection to the central or peripheral nervous
system of a subject in need of such neuroprotection.

32. The package of claim 31, wherein the amount of glatiramer
35 acetate is 300 mg.

33. The package of claim 31, wherein the amount of glatiramer acetate is 20 mg.

34. The package of claim 31, wherein providing neuroprotection
5 comprises treating a neurodegenerative disease.

35. The package of claim 34, wherein the neurodegenerative
disease is multiple sclerosis, amyotrophic lateral sclerosis,
acute disseminated encephalomyelitis, adrenleukodystrophy,
10 adrenomyeloneuropathy, Leber's hereditary optic atrophy, Human
Lymphotropic T-cell Virus I (HTLVI)-associated myelopathy,
acute viral encephalitis, aseptic meningitis, virus-induced
demyelination, demyelinating genetic diseases, transverse
myelitis, Progressive Multifocal Leukoencephalopathy, a
15 nutritional metabolic disorder, acute glaucoma, chronic
glaucoma, close-angle glaucoma, open-angle glaucoma, optic
neuritis or systemic lupus erythematosus.

36. The package of claim 35, wherein the neurodegenerative
20 disease is multiple sclerosis.

37. The package of claim 35, wherein the neurodegenerative
disease is amyotrophic lateral sclerosis.

25 38. The package of claim 35, wherein the neurodegenerative
disease is acute close-angle glaucoma.

39. The package of claim 35, wherein the neurodegenerative
disease is optic neuritis.

30 40. The package of claim 35, wherein the neurodegenerative
disease is systemic lupus erythematosus.

41. The package of claim 31, wherein providing neuroprotection
35 comprises treating neurotrauma.

42. The package of claim 41, wherein the neurotrauma is a result of a traumatic event selected from the group consisting of head trauma, spinal trauma, neurotoxic injury, eye injury, stroke, ischemia, hypoxia, and anoxia.

5

43. The package of claim 42, wherein the neurotrauma is a result of eye injury.

44. The package of claim 31, wherein providing neuroprotection comprises providing protection against toxic levels of glutamate.

45. The package of claim 31, wherein providing neuroprotection comprises providing protection against toxic levels of monoamine oxidase-B activity.

46. A pharmaceutical composition comprising an amount of glatiramer acetate and an amount of 2-amino-6-trifluoromethoxybenzothiazole, wherein the amounts when taken together are effective to provide neuroprotection to the central or peripheral nervous system of a subject in need of such neuroprotection.

47. The pharmaceutical composition of claim 46, wherein each of the amount of glatiramer acetate when taken alone and the amount of 2-amino-6-trifluoromethoxybenzathiazole when taken alone is effective to provide neuroprotection to the central or peripheral nervous system of the subject.

48. The pharmaceutical composition of claim 46, wherein either of the amount of glatiramer acetate when taken alone, or the amount of 2-amino-6-trifluoromethoxybenzathiazole when taken alone or each such amount when taken alone is not effective to provide neuroprotection to the central or peripheral nervous

system of the subject.

49. The pharmaceutical composition of claim 46, wherein
5 providing neuroprotection comprises treating a neurodegenerative
disease.

50. The pharmaceutical composition of claim 49, wherein the
neurodegenerative disease is multiple sclerosis, amyotrophic
lateral sclerosis, acute disseminated encephalomyelitis,
10 adrenleukodystrophy, adreno-myeloneuropathy, Leber's hereditary
optic atrophy, Human Lymphotropic T-cell Virus I (HTLVI)-
associated myelopathy, acute viral encephalitis, aseptic
meningitis, virus-induced demyelination, demyelinating genetic
diseases, transverse myelitis, Progressive Multifocal
15 Leucoencephalopathy, a nutritional metabolic disorder, acute
glaucoma, chronic glaucoma, close-angle glaucoma, open-angle
glaucoma, optic neuritis or systemic lupus erythematosus.

51. The pharmaceutical composition of claim 50, wherein the
20 neurodegenerative disease is multiple sclerosis.

52. The pharmaceutical composition of claim 50, wherein the
neurodegenerative disease is amyotrophic lateral sclerosis.

25 53. The pharmaceutical composition of claim 50, wherein the
neurodegenerative disease is acute close-angle glaucoma.

54. The pharmaceutical composition of claim 50, wherein the
neurodegenerative disease is optic neuritis.

30 55. The pharmaceutical composition of claim 50, wherein the
neurodegenerative disease is systemic lupus erythematosus.

56. The pharmaceutical composition of claim 50, wherein
35 providing neuroprotection comprises treating neurotrauma:

57. The pharmaceutical composition of claim 46, wherein the neurotrauma is a result of a traumatic event selected from the group consisting of head trauma, spinal trauma, neurotoxic injury, eye injury, stroke, ischemia, hypoxia, and anoxia.

57. The pharmaceutical composition of claim 57, wherein the neurotrauma is a result of eye injury.

58. The pharmaceutical composition of claim 46, wherein providing neuroprotection comprises providing protection against toxic levels of glutamate.

59. The pharmaceutical composition of claim 46, wherein providing neuroprotection comprises providing protection against toxic levels of monoamine oxidase-B activity.

60. A product containing glatiramer acetate and 2-amino-6-trifluoromethoxybenzathiazole as a combined preparation for simultaneous, separate or sequential use in therapy.

61. A product containing glatiramer acetate and 2-amino-6-trifluoromethoxybenzathiazole as a combined preparation for simultaneous, separate or sequential use to provide neuroprotection to the central or peripheral nervous system.

62. The use glatiramer acetate and 2-amino-6-trifluoromethoxybenzathiazole for the manufacture of a combined preparation medicament to provide neuroprotection to the central or peripheral nervous system, wherein glatiramer acetate and 2-amino-6-trifluoromethoxybenzathiazole are administered simultaneously, separately or sequentially.

63. The product or use of any one of claims 60-62, wherein the use is sequential at an interval of up to 24 hours.

5 64. The product or use of claims 63, wherein the interval is from 1 to 12 hours.

65. The product or use of claims 64, wherein the interval is 2 hours.

10 66. The product or use of any one of claims 60-62, wherein the use is separate.

67. The product or use of any one of claims 60-62, wherein the use is simultaneous.

15 68. The use 2-amino-6-trifluoromethoxybenzathiazole for the manufacture of a medicament to provide neuroprotection to the central or peripheral nervous system in a patient who is being treated with glatiramer acetate to provide neuroprotection.

20 69. The use 2-amino-6-trifluoromethoxybenzathiazole for the manufacture of a medicament to provide neuroprotection to the central or peripheral nervous system in a patient population that is being treated with glatiramer acetate for neuroprotection
25 therapy.

70. The use 2-amino-6-trifluoromethoxybenzathiazole for the manufacture of a medicament for the enhancement of neuroprotection
30 therapy in a patient who is being treated with glatiramer acetate to provide neuroprotection.

USE OF A COMBINATION OF RILUZOLE AND GLATIRAMER ACETATE
FOR NEUROPROTECTION

Abstract of the Disclosure

5 The subject invention provides a method of providing neuroprotection to the central or peripheral nervous system of a subject in need of such neuroprotection comprising periodically administering to the subject an amount of glatiramer acetate and an amount of 2-amino-6-trifluoromethoxybenzathiazole, wherein the
10 amounts when taken together are effective to provide neuroprotection to the central or peripheral nervous system of the subject. The subject invention also provides a package comprising glatiramer acetate, 2-amino-6-trifluoromethoxybenzothiazole and instructions for use together to provide neuroprotection to the
15 central or peripheral nervous system of a subject in need of such neuroprotection. Additionally, the subject invention provides a pharmaceutical composition comprising an amount of glatiramer acetate and an amount of 2-amino-6-trifluoromethoxybenzothiazole, wherein the amounts when taken together are effective to provide
20 neuroprotection to the central or peripheral nervous system of the subject. The subject invention further provides a pharmaceutical combination comprising separate dosage forms of an amount of glatiramer acetate and an amount of 2-amino-6-trifluoromethoxybenzothiazole, which combination is useful to
25 provide neuroprotection to the central or peripheral nervous system of the subject.